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10/820,099	04/07/2004	Simon McEwen	61190(50221)	8281

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EXAMINER	
HANLEY, SUSAN MARIE	
ART UNIT	PAPER NUMBER
1651	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/820,099	MCEWEN, SIMON	
	Examiner	Art Unit	
	SUSAN HANLEY	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-16,18-24 and 29-32* is/are pending in the application.

4a) Of the above claim(s) *30-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-16,18-24,29 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Newly submitted claim 32 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: New claim 32 is drawn to a composition for the treatment or prophylaxis of multiple sclerosis comprising beta-glucuronidase and myelin, the composition provided in a dose that provides a beneficial effect to an individual in need of treatment. This composition is distinct from the presently examined composition comprising collagen and beta-glucuronidase because the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the composition comprising collagen and beta-glucuronidase is for treating arthritis. Collagen is a structural protein that is indicated as an auto-antigen in RA. The newly claimed composition is for treating encephalomyelitis. Myelin is a fatlike substance composed of lipids and proteins that forms a sheath around the axons of some nerves. Thus, myelin and collagen are distinct substances with different structure and function. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants. It would be an undue burden to search both compositions because they contain two very different components (myelin vs. collagen) that have different structures, content and uses in the body. The different components are related to the treatment of different disease states.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution

on the merits. Accordingly, claim 32 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Withdrawal of Rejections

The rejections not explicitly restated below are withdrawn due to Applicant's response in the amendment filed 10/28/2009.

Specification

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: The disclosure of the composition of claim 29 is not taught in the specification.

The amendment filed 10/28/09 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The newly added Appendix to the specification contains New Matter related to data regarding the use of a composition comprising beta-glucuronidase and myelin to treat EAE.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Suggestion

It is suggested the concentration in claims 10 and 14 be expressed as "mg/L".

Claim Objections

Claim 4 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Beta-D-glucuronoside glucuronosohydrolase (EC 3.2.1.31) is simply the formal name for beta-glucuronidase. It does not provide a limitation that further describes the enzyme.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 4, 7, 8, 11, 12 and 15 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claimed compositions are drawn to a synovial fluid which is a product of nature.

Jacox (1955) discloses that beta-glucuronidase is present in the synovial fluid of persons with rheumatoid arthritis (abstract and Fig. 1, page 264; instant claims 1 and 11).

Nemeth-Csoka (1984) teaches that collagen or at least collagenous chains are present in synovial fluid. In arthrotic synovial fluids the collagenous chains, especially collagen type II and 1-alpha chains, exceed those of non-arthrotic ones (p. 691, right column; instant claims 1 and 11).

Houli (1959) discloses that glucose (line 7 of abstract; instant claims 11 and 12) and albumin (line 23 of abstract; instant claims 7 and 8; albumin is interpreted as an inert proteinaceous moiety) are present in the synovial fluid of persons having rheumatoid arthritis.

Jebens (1959) teaches that the pH of synovial fluid is 7.3 to 7.5 (instant claim 15).

Beta-D-glucuronoside glucuronosohydrolase (EC 3.2.1.31) is simply the formal name for beta-glucuronidase, as in instant claim 4).

Therefore the references teach that a synovial fluid that naturally has beta-glucuronidase, collagen, glucose and albumin at a neutral pH. The beta-glucuronidase and collagen are considered to be present in a dose that provides a beneficial effect to an individual in need of treatment. The specification does not provide a definition of "a beneficial effect to an individual in need of treatment". Hence, the amounts of beta-glucuronidase and collagen are reasonably considered to be in a beneficial amount.

Claim Rejections - 35 USC § 112

Claims 1, 4-16 and 18-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising collagen and beta-glucuronidase in a therapeutic composition in a dose which provides a beneficial effect to an

individual in need of treatment for rheumatoid arthritis, does not reasonably provide enablement for a composition comprising collagen and beta-glucuronidase in a therapeutic composition in a dose which provides a beneficial effect to an individual in need of treatment or prophylaxis for any type of arthritis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright,* 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

[1]As pointed out by the court in In re Angstadt, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands',* 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Exparte Forman,* 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,

6) the relative skill of those in the art,
7) the predictability of those in the art,
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108,427 F.2d 833,839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands" factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to a composition for the treatment or prophylaxis of arthritis comprising a therapeutic composition having beta-glucuronidase, collagen and other additives in claimed amounts and a kit thereof for the treatment or prophylaxis of arthritis.

The relative skill of those in the art is high, generally that of a medical doctor.

That factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher,* 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.,* 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702

(Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain).

There are many forms of arthritis with different and/or unknown causes. The Merck Manual classifies types of arthritis having vastly different etiologies. That is, arthritis can be caused by the immune system (rheumatoid arthritis), degenerative joint disease (osteoarthritis), can be associated with spondylitis or by infectious agents (The Merck Manual (pages 951 and 957). The symptoms of rheumatoid arthritis and osteoarthritis are very different (page 954). There are no known cures for any type of arthritis and the therapies for different types of arthritis are diverse and different.. For example, osteoarthritis can be treated by exercise, surgery and the administration of drugs such as NSAIDS or muscle relaxants (page 973, The Merck Manual). Rheumatoid arthritis is treated by bed rest, NSAIDS, salicylate, indomethacin, gold compounds, D-penicillamine etc. (The Merck Manual (pages 958-962).

Prophylaxis is the prevention of disease. Prevention means to keep something for happening for 100% of the time. There are no therapies known to prevent any type of arthritis.

There is no way for one skill in the art to know, a priori, if a given composition can treat or prevent any type of arthritis with a reasonable expectation of results. Thus, the state of the prior art does not support the broad scope of the above claims.

2. The breadth of the claims

The claims are broad insofar as they disclose a composition for the treatment or prophylaxis of arthritis.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification teaches that a mixture of collagen and beta-glucuronidase were used to treat mice that had been injected with collagen. McPeak et al. (US 2003/0118672) teach that this is a model for rheumatoid arthritis (US 20030118672; section [0088]). The specification demonstrates that administration of the mixture delayed the onset and ameliorated the symptoms of the induced arthritis (pages 8-12). The specification does not show that the induced disease was prevented. The specification does not provide disclosure or a working example that demonstrates the efficacy of the mixture in other forms of arthritis.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed supra) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that one could be predictably treat any type of arthritis with the claimed compositions or prevent any type of arteries from occurring in a person as inferred in the claims and contemplated by the specification.

Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

To practice the invention of the instant claims required undue experimentation due to

unpredictability in the treatment and prophylaxis of arthritic diseases and the lack of direction from Applicants. In light of the above discussion, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7-14 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7-10 are rejected because the phrase "stabilizer and/or activator" is vague. It is unclear what is being stabilized and/or activated.

Claims 10 and 14 are rejected because the ranges of up to 20 mg/l for the concentration of the stabilizer/activator and up to 20 μg/l for the concentration of the hydroxyl moiety, respectively, are conflicting. The claims indicate that a component is present but the inclusion of zero ("up to" includes zero in the range) implies that the component is not present.

Claims 11-14 are rejected because the phrase "hydroxyl moieties" is vague and indefinite. The term "moiety" means an entity that is part of the structure of something. The invention claimed is a composition. It is unclear what component comprises hydroxyl moieties. Claims 12 and 13 are inconsistent because the claims are directed to compounds that bear hydroxyl moieties. These compounds are not part of another structure.

Claim 20 is rejected because the use of parentheses around terms after the claim glycosaminoglycans is vague and indefinite. It is unclear if the limitation that appears in parentheses is part of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4, 7, 8, 11, 12 and 15 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Jacox et al. (1955) in light of Nemeth-Csoka et al. (1984), Houli et al. ((1959); abstract only) and Jebens ((1959); abstract only).

The claims are drawn to a therapeutic composition comprising beta-glucuronidase and collagen in a dose to provide a beneficial effect to an individual in need of treatment for arthritis.

The composition can further comprises an inert proteinaceous moiety and hydroxyl moieties that is a sugar. The pH of the composition can be neutral. The enzyme is beta-D-glucuronosohydrolase (EC 3.2.1.31).

Jacox discloses that beta-glucuronidase is present in the synovial fluid of persons with rheumatoid arthritis (abstract and Fig. 1, page 264; instant claims 1 and 11).

Nemeth-Csoka teaches that collagen or at least collagenous chains are present in synovial fluid. In arthrotic synovial fluids the collagenous chains, especially collagen type II and 1-alpha chains exceed those of non-arthrotic ones (p. 691, right column; instant claims 1 and 11).

Houli discloses that glucose (line 7 of abstract; instant claim 1, 11 and 12) and albumin (line 23 of abstract; instant claims 7 and 8; albumin is interpreted as an insert proteinaceous moiety) are preset in the synovial fluid of persons having rheumatoid arthritis.

Jebens teaches that the pH of synovial fluid is 7.3 to 7.5 (instant claim 15).

Therefore the references teach synovial fluid having beta-glucuronidase, collagen, glucose and albumin at a neutral pH. The beta-glucuronidase and collagen are considered to be present in a dose that provides a beneficial effect to an individual in need of treatment. The specification does not provide a definition of "a beneficial effect to an individual in need of treatment". Hence, the amounts of beta-glucuronidase and collagen are reasonably considered to be in a beneficial amount. The composition is therapeutic since it is in a therapeutic amount. and therefore therapeutic.

The disclosures by Nemeth-Csoka, Jebens and Houli are supporting references and properly used in a rejection under of U.S.C. 102 since they teach what is naturally present in synovial fluid. MPEP 2131.01.

Beta-D-glucuronosohydrolase (EC 3.2.1.31) is simply the formal name for beta-glucuronidase (instant claim 4).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4-16, 18-24 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Worth (2001) in view of Astarita et al. (1996; cited in the IDS filed 8/12/06), Fell et al. ((1990); cited in the IDS filed 8/12/08), McEwen ((1975): cited in the IDS filed 5/10/2004), Larche et al. (US 2006/0024335), Vischer ((1995; cited in the IDS filed 3/3/2006), Jefferson (US 5,268,463) and Klaus et al. (US 20010056069).

The claims are summarized supra. The composition can comprise a stabilizer and/or activator that is protamine sulfate at a concentration up to 20 mg/L. The composition can comprise 1,3-cylcohexane diol at a concentration up to 20 µg/L. The composition can be at a pH between 5 and 6. The collagen can be present in an amount between 0.5 and 2.5 mg/ml or at a concentration between 10 and 1 x 10^{15} molecules/ml. The composition can comprise chondroitin-6-sulfate in a concentration between 0.1 and 1.0 mg/ml. The composition is suitable for transdermal or intradermal injection. The composition can comprise beta-glucuronidase, collagen, protamine sulfate and 1,3-dyclohexane diol in the amounts specified in claim 29 at a pH of 5.9. The collagen and beta-glucuronidase can be provided as separate solutions in a kit.

Worth discloses that enzyme-potentiated desensitization (EPD) therapy has been used to successfully treat several forms of rheumatoid arthritis (RA). EPD therapy is administered by injection.

Worth does not disclose that an EPD composition for the treatment of RA comprises beta-glucuronidase and collagen, 1,3-cylcohexane diol, protamine sulfate, chondroitin sulfate in the claimed amounts, the claimed pH values of the compositions, that the composition is suitable for intradermal or transdermal injection or that the collagen and enzyme are supplied in solutions in a kit.

Astarita discloses that EPD therapy is a method of immunotherapy the comprises administering beta-glucuronidase and an allergen at a very low dose. The method was evaluated for the treatment of pollinosis wherein the allergen contains grass pollen (abstract). A composition comprising beta-glucuronidase (40 Fishman units; instant claims 1 and 11), 1,3-cyclohexane diol; 0.001 mg/ml) (instant claims 11-14), protamine sulfate (instant claims 7-10; 1 mg/ml) and chondroitin 6-sulfate (0.5 mg/ml; instant claims 19-22) and an allergen was administered intradermally (instant claim 23; page 249, right column, last paragraph). The method was found to be effective.

Fell discloses a single dose EPD for summer hay fever comprising administering a composition having 100 Fishman units of beta-glucuronidase and grass pollen to a person in need thereof. The therapy was shown to be an effective treatment (page 78, right col., third paragraph).

McEwen teaches the administration of beta-glucuronidase (400 U) with chondroitin sulfate, protamine sulfate, 1,3-dyclohexane diol, allergen and hyaluronidase for the EPD treatment of hay fever in mice and humans.

Therefore, the combined disclosures by Fell, McEwen, and Astarita teach that the amount of beta-glucuronidase can be optimized according to the needs of the therapy.

Larche discloses methods for desensitizing an individual by administering an antigenic polypeptide to treat a disease (abstract). Larche teaches that collagen is an auto-antigen in rheumatoid arthritis (section [0126]).The composition containing the antigen can be administered intradermally (section [0016]; instant claim 23). The dosage is adjusted to be effective in an escalating dosage regimen that can begin with 5 microgram of polypeptide (section [0105] and can be adjusted according to the circumstances (section [0106]).

Vischer discloses the oral desensitization of human immune diseases by the administration of an antigenic polypeptide. Collagen II is an antigen for rheumatoid arthritis. It has been administered at a dose of 0.1 mg daily for one month and then 0.5 mg daily for two months (instant claim 6; 0.6×10^{10} molecules, instant claim 18). Patients receiving the composition showed improvement (p. 156, right col., first paragraph).

Therefore, the combined disclosures by Vischer and Larche teach the administration of collagen as an antigen for the desensitization treatment of rheumatoid arthritis.

Jefferson discloses that the pH optimum of beta-glucuronidase is from 5.0 to 7.8 (col. 5, lines 26-28).

Klaus discloses that the molecular weight of the basic unit of collagen is 300,000 Da. Klaus is an evidence document used to teach the molecular weight of collagen.

It would have been obvious to one of ordinary skill in the art, a medical doctor, at the time the invention was made to use a composition comprising beta-glucuronidase, collagen, 1,3-cylcohexane diol, chondroitin-6-sulfate and protamine sulfate in the claimed amounts for the EPD treatment of rheumatoid arthritis. The ordinary artisan would have been motivated to employ the combination of beta-glucuronidase and collagen for EPD therapy because EPD therapy comprises the administration of beta-glucuronidase and an antigen for the treatment of a disease. An antigen and an allergen are interpreted as equivalents since they both cause an immunologic response in the body. Worth teaches that EPD has been used to treat RA. Collagen is a known auto-antigen of RA that has been used on its own for desensitization treatment of RA. Thus, it would be obvious to the ordinary artisan to employ beta-glucuronidase and collagen as the antigen since EPD treatment comprises the administration of beta-glucuronidase and an antigen. The ordinary artisan would have had a reasonable expectation that one could employ a composition comprising beta-glucuronidase and collagen for the EPD therapy of RA since Worth teaches that RA has been treated by EPD and other immune diseases related to sensitization by antigens have been successfully treated by the administration of beta-glucuronidase and an antigen.

It would have been obvious to one of ordinary skill in the art, a medical doctor, at the time the invention was made to make a composition comprising collagen, beta-glucuronidase, and the additives of 1,3-cyclohexane diol, protamine sulfate and chondroitin sulfate for the EPD therapy of RA. The ordinary artisan would have been motivated to make the composition with the additives because Astarita teaches that they are useful for compositions for EPD therapy. The ordinary artisan would have had a reasonable expectation that one could employ said additives in

combination with collagen and beta-glucuronidase because Astarita teaches the successful use of a an EPD composition comprising said additives, antigen and beta-glucuronidase for a diseases state related to sensitization by an antigen.

It would have been obvious to one of ordinary skill in the art, a medical doctor, at the time the invention was made to provide the composition of claim 29 in the claimed amount and to buffer the pH of the claimed compositions between 5 and 6, neutral pH or at 5.9. The ordinary artisan would have been motivated to optimize the amounts of the components of obtain the claimed composition at any of the claimed pH ranges or values in order to achieve the most effective composition for the EPD treatment of RA. An ordinary artisan would naturally experiment with the amounts of the components and the pH of the composition for EPD for the exploitation of success. The disclosures by Fell, McEwen, and Astarita (amount of collagen) and Larche and Vischer (amount of beta-glucuronidase) demonstrate that different amounts of the components have been employed and that the ordinary artisan would be motivated to optimize the amounts of the components to achieve an effective composition for the EPD of RA. Accordingly, it would have been *prima facie* obvious to one of skill in the art at the time the invention was made to optimize the amounts of the components of an EPD composition for RA at an appropriate pH, especially in the absence of an objective showing of unexpected results.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to provide separate solutions of beta-glucuronidase and collagen to be mixed together for administration for EPD therapy. The ordinary artisan would have been motivated to do so because the ordinary artisan would have known that the enzyme and the collagen must be formulated separately before they can be administered together. The ordinary artisan would have

been motivated to provide the solution is a kit for the sake of convenience. The ordinary artisan would have had a reasonable expectation that one could make separate solutions of collagen and beta-glucuronidase to be combined tougher because this it is a common lab procedure to make solutions of biochemicals.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUSAN HANLEY whose telephone number is (571)272-2508. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Susan Hanley/
Examiner, Art Unit 1651

/Irene Marx/
Primary Examiner
Art Unit 1651